MEDICAL SCIENCE

Rate and pattern of prescription for osteoporosis and non-alcoholic fatty liver disease among patients with diabetes mellitus in Tabuk City, Saudi Arabia

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ABSTRACT

Background: Diabetes mellitus, non-alcoholic fatty liver disease (NAFLD) and osteoporosis are common serious diseases with high morbidity and mortality. When co-exist they increase each other deleterious consequences. This is the first study to assess the same in Saudi Arabia. *Objectives:* The study aimed to assess the rate and pattern of prescription for osteoporosis and NAFLD among patients with diabetes mellitus in Saudi Arabia. *Methods:* This cross-sectional study was conducted among 84 diabetic patients (above 60 years of age) at the Diabetes Center, Tabuk City, Saudi Arabia during the period from August 2022 to January 2023. A structured questionnaire based on demographic data, duration of diabetes, exercise, HbA1c, macro vascular complications, smoking and Dual-energy x-ray absorptiometry (DEXA) scan was used. The Q-fracture risk was used to assess the risk of fracture, and NAFLD was assessed using ultrasonography. *Results:* There were 84 diabetic patients (52.4% were women and 80.5% were obese or overweight, central adiposity was found in 77.8%); mean age, 62.38±7.56 years, NAFLD was found in 45.2%, osteoporosis and osteopenia were present in 28.6% and 41.7% respectively. No patient was receiving osteoporosis treatment and the uptake of glucagon-like peptide agonists (GLP-1) agonists and sodium-glucose co transporter's inhibitors (SGLT-2) was negligible (4.8% and 7.1% respectively). *Conclusion:* Osteoporosis, osteopenia and NAFLD were prevalent among patients with diabetes in Tabuk city, Saudi Arabia. The uptake of osteoporosis treatment, GLP-1 agonists and SGLT-2 inhibitors was low. Physicians might need to strictly follow the treatment guidelines and screen patients with diabetes mellitus for osteoporosis.

Keywords: Osteoporosis, non-alcoholic fatty liver disease, prescription, diabetes mellitus, Saudi Arabia.

1. INTRODUCTION

Diabetes mellitus and osteoporosis are common serious diseases with high morbidity and mortality; the prevalence of diabetes is 10.5% globally and the Kingdom of Saudi Arabia is among the countries with the highest prevalence (Sun et al., 2022). Osteoporosis is common among patients with diabetes with a prevalence of 17.5% to 37.8% (Si et al., 2019). The prevalence of osteoporosis is expected to double by the year 2034 with an even greater rise in Asia, Africa and Latin America (Curtis et al., 2022). In Saudi Arabia, 63.6% of elderly men and 52.8% of women are suffering from the disease (Sadat-Ali et al., 2022). Al-Homood et al., (2017) conducted a study in Saudi Arabia and reported osteoporosis in 29.4% and osteopenia in 40% and intermediate-high fracture risk in 31.8%.

Despite the high prevalence of osteoporosis and the availability of effective treatment, a big gap exists in the uptake of osteoporosis medications (Kanis et al., 2021). Plausible explanations might be a lack of case findings and knowledge about the disease. In Saudi Arabia, the disease is on the rise and nearly two-thirds of the population was affected (Curtis et al., 2022). Bone mineral density might be misleading among patients with diabetes. Previous studies reported high bone mineral density among patients with diabetes mellitus despite the high fracture risk (Farooqui et al., 2021).

Metabolic associated fatty liver disease (MAFLD) is a highly prevalent multi-system disease (25%) is suffering from the disease globally. MAFLD is an important cause of chronic liver disease; liver cirrhosis and hepatocellular carcinoma, non-alcoholic steatohepatitis is expected to lead the causes of liver transplantation (Targher, 2020). Nonalcoholic fatty liver disease (the serious component of metabolic syndrome) the disease is widely ignored despite its lethal consequences. The situation is alarming in Saudi Arabia, (NAFLD, hepatic fibrosis, hepatocellular carcinoma is expected to double by the year 2030 with an estimate of 204,000 liver-related death (Sanai et al., 2021). In addition, patients with NAFLD (both children and adults) had a high rate of osteoporosis, the released cytokines from the liver, vitamin D and sedentary life are to blame (Yilmaz, 2012). Literature regarding osteoporosis and NAFLD among type 2 diabetic patients scarce in Saudi Arabia. Thus, the current study evaluated the rate and pattern of prescription for osteoporosis and NAFLD among patients with diabetes mellitus in Tabuk city, Saudi Arabia.

2. METHODS

This cross-sectional study carried out on 84 diabetic patients (males and females above 60 years of age) at the Diabetes Center at King Fahad Specialty Hospital, Tabuk City, Saudi Arabia. The diabetic patients who come for regular follow-ups were randomly approached. The Diabetes Center is the reference center in Tabuk and receives a referral from all the Hospitals and Primary Health Centers and serves around 12000 patients. The study was conducted during the period from August 2022 to January 2023.

The sample size was calculated using the formula: n = Z2 P – Q/d2, where Z = 95% confidence (1.96), P = Diabetes prevalence in Saudi Arabia (Sun et al., 2022), Q = 100–prevalence and d = tolerated error.

A face-face interview was conducted with the participants. A meeting was held with the participants and the purpose of the project was detailed to them in the meeting. A structured questionnaire based on demographic data, duration of diabetes and level of exercise, smoking, Q-fracture risk assessment, ultrasonography and the metabolic-related fatty liver disease components was used to collect the data. Diabetes medications, the last glycated hemoglobin and diabetes macro vascular complications were collected from the patient's records.

The weight and height of all the participants were measured, and the body mass index (BMI) was calculated using the formula: BMI=Weight in Kg/ (Height in meters) ^{2}. A body mass index between 25 and 29 is regarded as overweight, while obesity was defined as a body mass index of 30-40.

Osteoporosis and osteopenia diagnosis

Dual-energy x-ray absorptiometry (DEXA scan) at the femoral neck, total neck and lumbar spines was used to diagnose osteoporosis and osteopenia. A score of ≤ -2.5 was used to diagnose osteoporosis and a score between -1 and -2.4 was regarded as osteopenia (Al-Homood et al., 2017). Fracture risk was measured by The Q fracture risk assessment tool. The tool was chosen because it controls for diabetes mellitus unlike other measures. The assessed age, gender, ethnicity, diabetes and chronic diseases including heart, pulmonary, endocrine, kidney diseases, liver disease, Parkinson's disease rheumatic disease and mal absorption. History of fracture and falls, antidepressant and contraceptives pills were included (Hippisley-Cox and Coupland, 2021).

Non-alcoholic fatty liver disease (NAFLD) or metabolic-associated fatty liver disease diagnosis

NAFLD was diagnosed by ultrasound scan and the presence of two or more metabolic-associated fatty liver disease criteria, the criteria are: Triglycerides ≥ 150mg, high-density lipoproteins ≤ 40mg in men or ≤ 50mg in women, waist > 102cm in men and >88 in

women, blood pressure ≥ 130/85, diabetes or pre diabetes in addition to use of antidiabetic, dyslipidemia and hypertensive medications (Targher, 2020; Sanai et al., 2021; Eslam et al., 2020).

Ethical consideration

Participants were asked to sign a written informed consent and an approval letter was obtained from the ethical committees of the University of Tabuk (reference number, UT-131-4-2021, dated, 14/1/2021).

Statistical analysis

The Statistical Package for Social Sciences (SPSS, IBM, Version 23, New York) was used for data analysis. The data were presented as percentages or meant SD unless otherwise specified. The Regression Analysis (Binary Logistic) was carried out to evaluate the relationship between fatty liver disease, age, sex, HbA1c, duration of diabetes and body mass index.

3. RESULTS

There were 84 diabetic patients (52.4% women); endocrine disease was reported in 7.1%, heart disease in 26.2% and NAFLD in 45.2%. Osteoporosis and osteopenia were present in 28.6% and 41.7% respectively. The above results imply that the patient is at high risk of morbidity and mortality. The mean age of the participants was 62.38±7.56 years, the duration since the diagnosis of diabetes was 13.97±9.39 years and the glycated hemoglobin was 8.15±1.87. The serum triglycerides, cholesterol and HDL were 154.68±85.4, 183.58±53.6 and 43.19±10 respectively. The waist circumference of the participants was 104.67±13.01cm, the body mass index was 29.82±6.05, the Q fracture score was 5.57±2.94, while the Q fracture score at the hip was 2.49±2.11. In the present study, 80.5% of the patients were obese or overweight, 77.8% had abnormal waist circumference and more than two-thirds had poor glycemic control. The above data showed an elderly population with multiple cardiovascular risk factors including obesity and abnormal waist circumference. They are at a high risk of fracture, mortality and morbidity (Table 1).

Table 1 Characters of eighty-eight diabetic patients

Character	No%
Males/Females	40 (47.6%)/44 (52.4%)
Endocrine disease	6 (7.1%)
History of fall	16 (19%)
Heart disease	22 (26.2%)
Chronic obstructive pulmonary disease	6 (7.1%)
Renal disease (grades 4 and 5)	8 (9.5%)
Chronic liver disease	4 (4.8%)
Fatty liver	38 (45.2%)
Osteoporosis	24 (28.6%)
Osteopenia	35 (41.7%)
Ten years fracture risk	18 (21.4%)
Abnormal waist circumference	66 (77.8%)
Obesity	36 (43.9%)
Overweight	30 (36.6%)
Poor glycemic control	57 (67.8%)
Character	mean± SD
Age	62.38±7.56
HbA1c	8.15±1.87
Diabetes duration	13.97±9.39
Cholesterol	183.58±53.6
Triglyceride	154.68±85.4
High-density lipoproteins	43.19±10
Alanine aminotransferase	24.45±12.82
Aspartate aminotransferase	23.42±12.42

Vitamin D levels	28.42±15.88
Systolic blood pressure	138.73±29.52
Diastolic blood pressure	76.54±11.08
Waist circumference	104.67±13.01
Body mass index	29.82±6.05
Q fracture score all	5.57±2.94
Q fracture score hip	2.49±2.11

In the present study, 57.1% of patients were on metformin, 28.6% on sulphonylureas, 21.4% on DPP-4 inhibitors, 61.9% were prescribed statins, 59.5% were on antihypertensive medications, 42.9% were on insulin. The uptake of SGLT-2 inhibitors, GLP-1 agonists and vitamin E was low at, 7.1%, 4.8% and 4.8% respectively. The above prescription is not in line with the recent guidelines. More use of SGLT-2 inhibitors and GLP-1 agonist for suphonylureas and insulin is needed (Table 2).

Table 2 The pattern of prescription among type 2 diabetic patients

Character	No%
Metformin	48 (57.1%)
Sulphonylureas	24 (28.6%)
DPP-4 inhibitors	18 (21.4%)
Insulin	36 (42.9%)
SGLT-2 inhibitors	6 (7.1%)
GLP-1 like agonists	4 (4.8%)
Statins	52 (61.9%)
Antihypertensive medications	50 (59.5%)
Vitamin E prescription	2 (4.8%)

The majority of patients were advised to follow an exercise of 30 minutes for five days/week (90.5%) and they were compliant, however, adherence to a healthy diet was observed in only 50%. Alarmingly, 97.6% of patients thought that fatty liver is a part of obesity (benign disease) and only 38.1% knew that non-alcoholic fatty liver disease might end in chronic liver disease (Figure 1, 2).

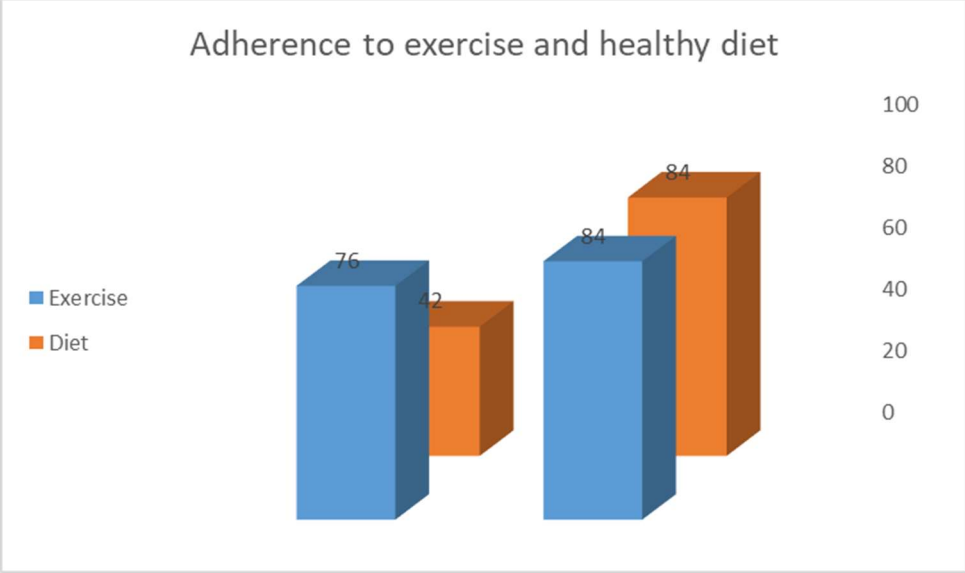

Figure 1 Adherence to diet and exercise among type 2 diabetic patients

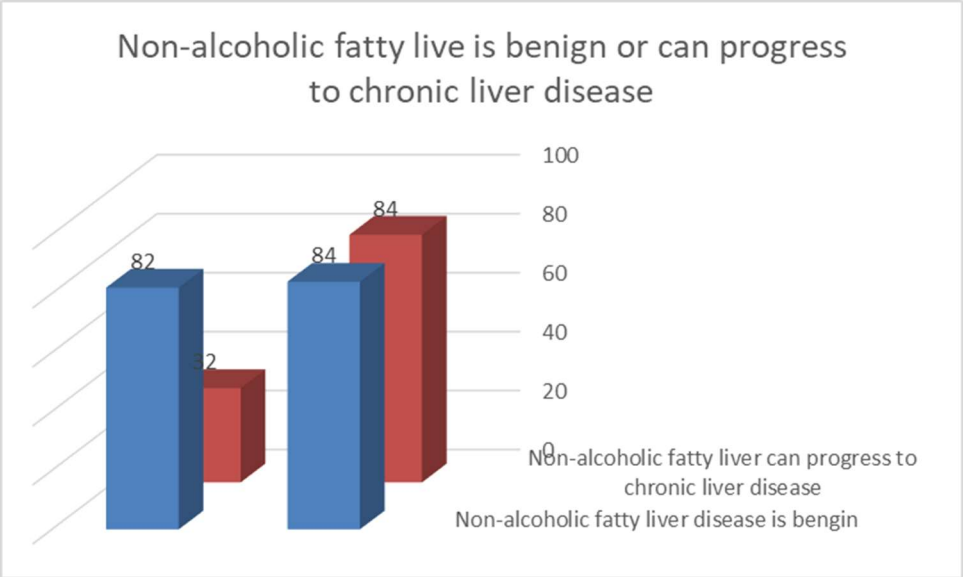

Figure 2 Patient's knowledge about non-alcoholic fatty liver disease

Regarding the criteria of MAFLD: Triglycerides ≥ 150mg was present in 32.5%, high-density lipoproteins ≤ 40mg in men or ≤ 50mg in women was present in 40 of patients, blood pressure ≥ 130/85mm hg was observed in 59.5%, while waist > 102cm in men and >88 in women was found in 66.7%. Table 3 depicted the percentages and numbers of MAFLD criteria.

Table 3 Metabolic-associated fatty liver disease criteria among type 2 diabetic patients

Character	No%
Triglycerides ≥ 150mg	26 (32.5%)
High-density lipoproteins ≤ 40mg in men or ≤ 50mg in women	32 (40.0%)
Statins use	52 (61.9%)
Use of antihypertensive medications	50 (59.5%)
Blood pressure ≥ 130/85	50 (59.5%)
Waist > 102cm in men and >88 in women	66 (77.8%)
Two criteria of MAFLD fulfilled	12 (14.3%)
Three criteria of MAFLD fulfilled	18 (21.4%)
Four criteria of MAFLD fulfilled	10 (23.8%)
Five criteria of MAFLD fulfilled	10 (23.8%)
Six criteria of MAFLD fulfilled	08 (9.5%)
Seven criteria of MAFLD fulfilled	06 (7.1%)
Non-alcoholic fatty liver disease	38 (45.2%)

In the present study, fatty liver was associated with body mass index, 95% *CI*, 0.0-0.19, P-value, 0.013, no association was found between fatty liver disease, sex, 95% *CI*, 0.0-10.08, P-value, 0.148, HbA1c, 95% *CI*, 0.60-2.97, P-value, 0.720, diabetes duration, 0.84-1.43, P-value, 0.492, O fracture score, 95% *CI*, 0.004-1.52, P-value, 0.076 (Table 4).

*__Table 4__ The relationship between the fatty liver, Q fracture score, HbA1c, diabetes duration, body mass index and sex

Character	B	Wald	95% *CI*	P-value
Sex	-6.49	2.09	0.0-10.08	0.148
HbA1c	0.29	0.51	0.60-2.97	0.720
Diabetes duration	0.94	0.47	0.84-1.43	0.492
BMI	-7.85	6.13	0.0-0.19	0.013
Q score	-2.57	2.83	0.004-1.52	0.076
Constant	7.75	2.43		0.119

*Binary logistic regression analysis

4. DISCUSSION

In the present study, osteoporosis and osteopenia were found in 28.6% and 41.7% of type 2 diabetic patients respectively, the current findings were lower than Sadat-Ali et al., (2022) who conducted a study in Eastern Saudi Arabia and reported a prevalence of 58.2%. A study conducted among women with diabetes in Riyadh, Saudi Arabia found osteoporosis and osteopenia in 29.1% and 40% respectively and in similarity to the current findings (Al-Homood et al., 2017). The present data are in line with a previous study published in the Eastern province, which reported a prevalence of osteoporosis of 34% in women and 30.7% in men (Alfadhli et al., 2022). A more recent study Dytfeld and Michalak, (2017) found osteoporosis in 34% and osteopenia in 50.1% in agreement with our findings. In addition, previous studies conducted in Saudi Arabia and China found that diabetes mellitus is the main factor affecting bone mineral density (Zhou et al., 2010; Coker et al., 2022). The authors reported that the majority of patients with osteoporosis (62.9%) were suffering from diabetes or abnormal glycemic parameters. The above results imply that osteoporosis and diabetes mellitus usually coexist. Urgent interventional measures are needed to raise awareness among patients and treating physicians.

Diabetes and NAFLD

In the present study, NAFLD was reported in 45.2% of patients with type 2 diabetes. A recent study showed that one-third of the Saudi population will suffer from diabetes before the age of 40 years and that obesity-related liver disease is rising at an alarming rate and is expected to cost six pillions/per year (Dytfeld and Michalak, 2017). Importantly Al-Humayed et al., (2020) and Alamri et al., (2021) reported a prevalence of NAFLD of 40% to 73.4% among patients with diabetes in Saudi Arabia. Al-Humayed et al., (2020) and Alamri et al., (2021) are in agreement with the current findings. The prevalence found in Saudi Arabia is similar to a study conducted in another Gulf country (68.1%) (Mohamed et al., 2022). A study conducted in Germany showed a lower prevalence (7.8%). The discrepancies in the prevalence might be explained by the different demographic factors, body weight and other comorbidities.

The coexistence of NAFLD and diabetes act synergistically to increase the lethal consequences, namely chronic liver disease, hospitalization, hepatocellular carcinoma and death (Labenz et al., 2022). In addition, the presence of NAFLD with diabetes increases atherosclerosis through dyslipidemia, high blood pressure and poor glycemic control (Bril, 2020). International guidelines for NAFLD screening are not uniform; the European guidelines are with screening. However, the American guidelines is not recommending screening due to the uncertainty about what to do with the results, cost-effectiveness of screening and the role of pharmacological intervention (Chalasani et al., 2018).

Bone mineral density among patients with NAFLD and diabetes

Previous studies conducted among patients with diabetes and NAFLD showed that patients with advanced fibrosis had a higher rate of osteoporosis. Mantovani et al., (2019) found that advanced fibrosis leads to decreased bone turnover and increased fragility. A recent study found a significant discrepancy in metabolism and bone biomarkers among patients with diabetes with and without NAFLD (Wang et al., 2022). The above implies that there is a significant interaction between bone, adipose tissue and the liver.

In this study, 80.5% of patients were obese or overweight and 77.8% had central adiposity, in addition, a high rate of cardiovascular risk factors was observed. The uptake of antidiabetic medications with cardio renal protection was very low (4.8% and 7.1% for glucagon-like peptide agonists and sodium-glucose co transporter's inhibitors). In addition, 42.9% of patients were on insulin despite the high risk of falls and high body mass index. An urgent call for adherence to the guideline of diabetes management is needed.

Importantly, patients with osteoporosis were not receiving osteoporosis treatment and the uptake of glucagon-like peptide agonists and sodium-glucose co transporter's inhibitors was negligible. The situation is alarming in Tabuk City. Eighty percent were obese, had cardiovascular risk factors and affected with NAFLD and they were not on drugs licensed for both obesity and diabetes mellitus (GLP-1 agonists). Glucagon-like peptide agonists and SGLT-2 inhibitors were shown to reduce liver enzymes, bilirubin and liver fibrosis (Mantovani et al., 2019). Policymakers and physicians in Tabuk city need to adhere to the most recent guidelines for better management strategies. Adherence to guidelines will improve diabetes control; reduce obesity and NAFLD complications and vascular risk.

The confusing tale of propensity to fracture and bone mineral density among type 2 diabetic patients

In this study, no differences were found between osteoporosis and fracture risk (28.6% versus 21.4%); our findings were in line with (Dytfeld and Michalak, 2017). On the other hand, Yamamoto et al., (2009) and Ohira et al., (2020) found higher rates of fractures

among patients with diabetes compared to their counterparts without the disease indicating the need for FRAX adjustment for diabetes. The temporal profile of diabetes is important and some studies found that diabetes might be protective against fracture initially and predispose to fracture after 5-10 years, the authors explained their findings by the increased fat mass (Löffler et al., 2021; Mitchell et al., 2018; Mitchell et al., 2021). The above findings indicate that the fracture risk is related to bone quality. Adjustment for diabetes and the use of Quantitative Computed Tomography might be solutions for the underestimated fracture risk among type 2 diabetic patients (Martínez-Montoro et al., 2022).

The current study's strength is that we screened eligible patients for osteoporosis and did not merely include patients who were refereed for Dual-energy x-ray absorptiometry scan. In addition, we use the Q fracture score that controlled for diabetes mellitus in contrast to FRAX fracture risk that under estimate the risk of fracture (Hippisley-Cox and Coupland, 2012). The study limitation was the small sample and the fact that the study was conducted at a single tertiary hospital. Thus, generalization to the whole Kingdom of Saudi Arabia cannot be insured.

5. CONCLUSION

The current study showed that osteoporosis, osteopenia and NAFLD were prevalent among patients with diabetes in Tabuk city, Saudi Arabia. The majority of the participants was obese with poor glycemic control and had high cardiovascular risk factors. Importantly, the patients were not taking treatment for osteoporosis. The uptake of glucagon-like peptide agonists and sodium-glucose co transporter's inhibitors was low. Nearly one third of the patients were on sulphonylureas and nearly a half was on insulin despite the high body mass index. Osteoporosis was correlated with body mass index, no correlation was found between osteoporosis and other parameters. Adherence to the treatment guidelines and screening patients with diabetes mellitus for osteoporosis is highly needed.

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Author Contributions

All authors contributed evenly with regards to development of study design, data collection and analysis, interpretation of data, drafting the manuscript and critical revision.

Informed consent

Informed consent was obtained from all individual participants included in the study.

Ethical approval

An approval letter was obtained from the ethical committees of the University of Tabuk (reference number, UT-131-4-2021, dated, 14/1/2021).

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Conflict of interest

The authors declare that there is no conflict of interests.

Data and materials availability

All data sets collected during this study are available upon reasonable request from the corresponding author.

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